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TechFlash: Wearable sensors and AI algorithms for ambulatory ECG analysis

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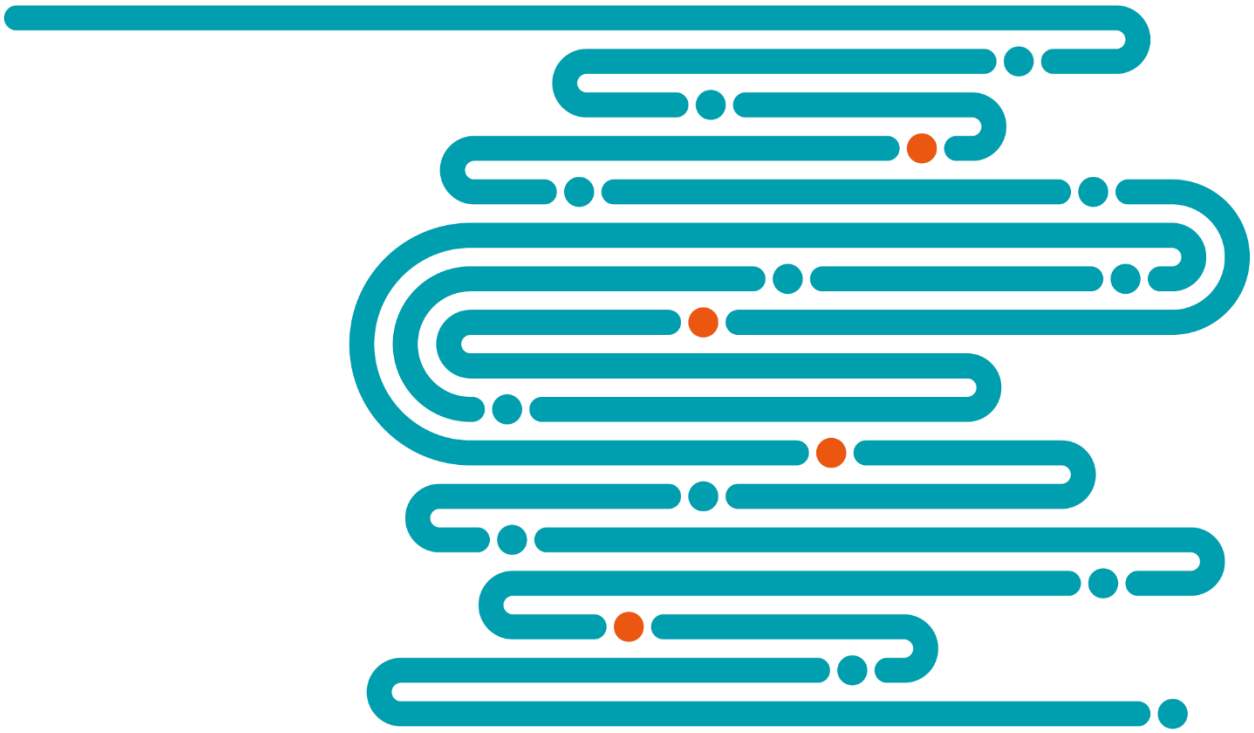

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This report comprises a review of abstracts identified through a search of the recent biomedical literature and does not constitute a comprehensive analysis. The report focus is on clinical evidence and outcomes.

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Technology overview and status

Artificial intelligence (AI) and wearable sensors are two rapidly emerging healthcare technologies poised to transform cardiology care. In combination, these technologies can capture a high-quality electrocardiogram (ECG) and automatically interpret the signal with cardiologist-level accuracy.[1-3] Many different arrhythmias, like atrial fibrillation (AF), may be detectable and their diagnosis could have important therapeutic implications and improve patient outcomes.

There are a large number of emerging technologies for ambulatory arrhythmia detection.[4] These ECG remote monitoring (RM) technologies can acquire, store, transmit (intermittent or continuous) and/or facilitate analysis of arrhythmias. There are many different ways, however, to accomplish these tasks. Those processes and technologies that are the most accurate, reliable and user-friendly may be critical for at-home adherence to data collection, long-term patient satisfaction and ultimately better patient outcomes.

Mobile ECG sensors have been incorporated into handheld devices (AliveCor Kardia), patches (iRhythm Zio), smartwatches (Apple Watch), fitness bands (Fitbit Sense), necklaces (toSense CoVa), rings, clothing and other wearable forms. Some important considerations for device selection may include electrode type and configuration, power consumption, battery life, memory capacity, signal processing electronics and wireless communication capability.[4, 5] Most mobile RM devices use a single lead ECG configuration for ease-of-use, but configurations with six or more leads (e.g., AliveCor KardiaMobile 6L) are also available.

The communication and information technology associated with ECG remote monitoring is currently undergoing rapid evolution in parallel with the rapid advances overall in digital technology, electronic miniaturization, microprocessor chip design, mobile smart devices, high speed networks (e.g., 5G) and other wireless technologies (e.g., Bluetooth). In particular, there is a rapidly growing trend for devices that utilize mobile smartphone technologies for data capture, storage and transfer.[6-8] Mobile phone-enabled technologies, also known as mHealth technologies, include numerous currently available apps and associated sensors for pulse and arrhythmia detection.[9]

Remote monitoring of physiologic parameters can result in overwhelming amounts of patient data that must be interpreted in a timely manner.[10] AI-based algorithms are quickly becoming the standard method for ECG analysis. These AI programs can be standalone device-agnostic software (Cardiologs ECG analysis) or integrated software intended for use with specific sensors and technology. Due to high computing power demands, complex AI algorithms often require specialized hardware at a centralized location working on batched ECG data uploaded to cloud storage.

Machine learning (ML), neural networks and deep learning (DL) are special subsets of AI and are some of the most powerful types of AI for ECG analysis.[11, 12] (See Figure 1) Notably, ML is fundamentally different from conventional computer programs in that it doesn't require explicit programming instructions, like a specific threshold for an ECG interval; rather, the machine "learns" what features of the ECG signal are important for diagnosis, usually by being trained on a large annotated data set in a process called supervised learning.

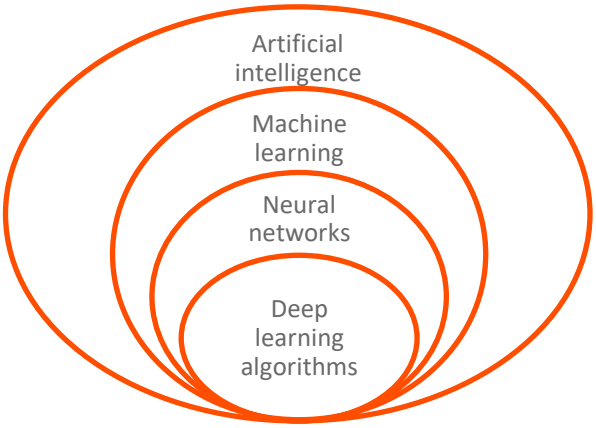

Figure 1. The relationship between AI terminology. Machine learning/deep learning are specific types of AI.

ML/DL algorithms for ECG analysis have some inherent strengths and weaknesses.[13] For example, the accuracy and effectiveness of ML can continue to improve over time as it is exposed to more data through supervised learning. Currently available annotated ECG data sets used for algorithm training may include hundreds of thousands of patients and associated ECGs. On the other hand, a noted weakness of deep learning algorithms is that the hidden layers of the programming model may involve complex and non-linear relationships; thus acting like a black box obscuring the ability to explain how the AI algorithm reached its conclusion.

Whenever AI is used in a clinical care pathway, it becomes a de facto medical technology; therefore, it should be subject to the same evaluation standards used for other types of medical devices. Both the AI analysis platforms and sensors should have the relevant Food and Drug Administration (FDA) clearance to ensure they meet safety, accuracy and quality standards. Many mobile ECG devices and AI-based ECG algorithms have already received FDA marketing clearance and many more are in the pipeline.[14] Specific product labeling may be critical to understand the validated patient criteria (e.g., whether the subject has a previous diagnosis of AF) or device criteria (e.g., accurate only for heart rates > 50 bpm but <150 bpm).[9]

Due to rapid developments in mHealth and AI technologies, the FDA process for approving these devices is still evolving. The current FDA approach to AI is risk-based, with more requirements for technologies that are used with limited clinician oversight and/or for medical purposes and fewer requirements for technologies that simply streamline workflow or are used for fitness tracking.[15] Current FDA approaches are also based on a balance between ensuring technology safety without suppressing innovation.[16, 17] Some FDA regulations/guidance that may apply include those for software as a medical device (SAMD), AI/ML in software and mobile medical applications (MMA).

A regulatory issue arises from the capability for AI applications to continue to learn, hence change their accuracy and diagnostic power, following initial clearance. Continued learning is presumably good, but instances where AI develops biases over time due to limitations in the learning data set are also possible.[18] So far, AI learning tends to be locked after approval, with enhancements due to new learning requiring a new approval process.

Technology significance

The ECG is one of the most common tests used in cardiology. Its main purpose is to diagnose abnormal heart rhythms associated with primary heart disease or other diseases with secondary effects on the heart rate and rhythm. Due to its widespread use, any emerging technology involved in ECG monitoring is potentially very high impact.

AF is one of the most common cardiac arrhythmias detected by ECG and it is a significant source of patient morbidity, mortality and utilization of healthcare resources in the US.[19-23] For example, the presence of AF is well known to increase the risk of ischemic stroke by ~2x to 5x. AF is further estimated to affect ~3 to 6 million Americans with a prevalence that increases steadily with age (~0.1% for <55 years to ~9.0% for >80 years) and is therefore increasing with the demographic aging of the population. Overall, AF may be the cause of about 3% to 4% of emergency department (ED) visits, result in more than 500,000 hospitalizations, contribute to >100,000 deaths and cost the US healthcare system more than $26 billion annually.[24, 25]

Unfortunately, AF may go undiagnosed in many patients until it causes a cryptogenic stroke.[26, 27] Early diagnosis, however, could lead to anticoagulation therapy that reduces the risk of stroke. Current strategies for AF detection may rely on short periods of ECG monitoring in the hospital/doctor's office or ambulatory

Holter monitoring for a few days. But due to its often paroxysmal and asymptomatic presentation, these methods may miss the presence of AF in many cases. Options for longer term monitoring may be expected to yield more diagnoses of AF and better describe the overall AF burden. Other barriers to implementation of conventional techniques include patient discomfort due to device wear, inconvenience and impedance of daily activities.

Small, wearable devices may provide a convenient, available option for ECG sensors that reduce discomfort and improve compliance, wear duration and patient satisfaction. Further, these devices may capture more relevant cardiac events not occurring during conventional short-term monitoring sessions. AI-enabled ECG algorithms can also provide caregivers the capability to rapidly sift through the large amounts of data provided by remote monitoring and triage important findings for clinician overread. When successful, the combination of wearables and AI analysis have the potential to transform cardiology care by enabling personalized medicine based on better monitoring of unique patient parameters.[13]

Disadvantages of wearable ECG sensors may include variable signal quality, a limited number of closely spaced electrodes and issues with the accuracy of AI analysis. Due to the latter, human oversight is still necessary. In addition, the presence of AI analysis can bias human overreading of some events and bias can also be introduced from the training data set itself. Similar to other emerging innovative technologies, lack of clinical experience with the technology may require extra validation steps and further clinical evidence development is needed.

Current practice and alternatives

Cardiac arrhythmias may comprise any slow, fast, irregular or abnormal rhythms. For example, ambulatory ECG analysis may identify normal sinus rhythm, bradycardia, tachycardia, AF, premature ventricular contractions (PVCs), supraventricular ectopy (SVE), atrioventricular block (AV block), wide QRS and signs of myocardial infarction or ischemia. The clinical significance of the various arrhythmias may range from benign to life-threatening and may be asymptomatic or associated with symptoms like fatigue, syncope, dizziness, palpitations and angina.

Some options for ambulatory ECG monitoring include Holter monitors, external loop recorders and internal loop recorders. (See Table 1) Holter monitors vary by manufacturer but typically include multiple adhesive wired electrodes (1 to 12 leads) connected to a small recorder device providing continuous data collection. Holter monitor wear time is typically 24 to 48 hours, but may be expanded in some cases. At the end of the monitoring period, the recorder is collected for data analysis. Some Holter monitors are not waterproof so the patient may not bathe during monitoring or the device must be removed for showering. The multiple connected wires are also considered uncomfortable by some patients and can frequently become detached.

Loop recorders collect a short period of ECG data before and after the device is activated by the patient due to symptoms or the device may be auto-triggered by pre-programmed parameter thresholds. These devices may be external (typically with one or two leads) or implanted subcutaneously (single-lead) as a completely internal cardiac monitor with transcutaneous activation and/or interrogation (e.g., Medtronic Linq, Boston Scientific Lux-Dx, Abbott Confirm Rx, Biotronik BioMonitor).

External loop recorders may be used for intermediate durations ranging from a few weeks to a few months and internal loop recorders may be used for longer periods for months or even years. Longer wear periods for external devices may require battery recharging and electrode replacement. Alternatively, some external devices may use non-adhesive dry electrodes on a chest strap or belt. Internal devices are the most costly

and invasive, but may be useful for non-compliant patients and can readily collect data during sleep and other asymptomatic events.

As noted, arrhythmia/symptom frequency is one of the important considerations for device selection. For example, short-term Holter monitoring may be appropriate for initial monitoring with longer term monitoring options considered for infrequent events or when other options are unsuccessful for diagnosis.[5] Cost, invasiveness, patient comfort and compliance may be other deciding factors.

mHealth options for external ECG event recording are rapidly emerging.[5] These typically involve user-initiated collection of a short ECG segment after a symptom is detected or on a periodic schedule (e.g., once daily). These devices mostly use single-lead non-adhesive, re-useable electrodes on a handheld, smartwatch, fitness band or other wearable form. Data is uploaded to a smart phone for display, storage and analysis. These devices have the advantage of convenience, availability and comfort. Some simple types of arrhythmia analyses, like AF detection, may be done in real-time. Disadvantages include the need for patient recognition of an event, lack of continuous data and single lead configuration.

AliveCor KardiaMobile is an example of a handheld smartphone-enabled ECG event recorder. (See Figure 2) The fingers on opposite hands are placed on the electrode pads for a single lead recording and a six lead recording can also be made with an optional electrode on the back of the device placed against the skin of the left leg. AliveCor has received FDA 510(k) clearances for the monitoring devices, apps, workstation and an AI analysis algorithm (KardiaAI). The latter is capable of reporting some parameters in real time and is cleared to detect AF, bradycardia, tachycardia, normal sinus rhythm and sinus rhythm with SVE, PVCs or wide QRS. Capability to detect elevated blood potassium levels (Kardia-K) using the AI platform is also in development and this app has received FDA breakthrough device designation to facilitate FDA clearance.

Figure 2. KardiaMobile ECG. AliveCor, Inc.

Other similar handheld devices with finger electrodes, like AliveCor, are available for ECG recording.[4] Some examples include HeartCheck Palm, HeartCheck CardiBeat, Cardiac Designs ECG Check, Lohman AfibAlert, Dimetek Dicare and HeartCheck Bodimetrics. These may vary in configuration and analysis capabilities. Some are intended to simply capture the ECG, store it and transfer it to a clinician. Other devices include built-in monitor and electronics, so they do not require a smartphone.

Smartwatches may also be used as intermittent ECG event recorders and they are rapidly growing in availability. These typically collect a single lead ECG using electrodes on the back of the watch in contact with the wrist and a finger on the opposite arm touched to the watch crown electrode. The Apple Watch Series 4, 5 and 6 have an FDA cleared ECG app that can capture a 30-second ECG segment and analyze it for normal rhythm and AF using a smartphone. ECG readings may be user-initiated in response to symptoms. Alternately, notifications may be automatically sent suggesting a possible irregular rhythm based on low or high pulse rate that doesn't agree with measured activity levels.

Similarly, the Samsung Galaxy Watch3 and Galaxy Watch Active2 have an FDA cleared ECG monitoring capability that includes screening for AF and Fitbit sense is another smartwatch type device with FDA clearance for AF detection. Smartwatches often combine ECG data with monitoring of other physiologic parameters and have simplified data storage and transmission capabilities using built in communication technologies and apps.

Patch-based sensors have multiple applications in arrhythmia detection and their use is also growing rapidly. Patch sensors are typically single lead and adhesively placed on the chest. Events and symptoms can be marked by pressing the top of the device. For example, the iRhythm Zio patch monitors (models XT and AT) can be used for continuous ECG collection for up to 14 days. (see Figure 3) The device is waterproof and is worn continuously during exercise, sleep and showering. The more recent Zio AT is intended for mobile cardiac telemetry (MCT) of higher risk patients and includes smartphone connectivity with daily data upload, analysis and alerts. Zio XT is intended as a longer-term alternative to Holter monitoring (14 days vs. 2 days) with collection of the device and analysis of the data at the end of the monitoring period. Preliminary ECG data analysis is performed using an FDA cleared deep learning algorithm and a final report is further validated with human overread by certified clinicians.

Figure 3. Zio patch.
iRhythm Technologies, Inc.

Preventice Solutions (recently purchased by Boston Scientific) also has a line of ECG monitors, called BodyGuardian, that includes waterproof devices, patches and single or multiple electrode configurations with reported battery life up to 16 days. The ECG devices are connected to a cloud-based, EHR-integrated central monitoring platform. A proprietary deep learning algorithm (BeatLogic) is used for ECG data analysis.

Similarly, Bardy Diagnostics Carnation Ambulatory Monitor (CAM) is a patch-based device placed along the central sternum for enhanced p-wave detection. (See Figure 4) Biotelemetry (recently purchased by Philips) also has patch-based devices (MCOT and ePatch) for mobile cardiac telemetry and longer term cardiac monitoring.

Figure 4. CAM patch.
Bardy Diagnostics, Inc.

VitalConnect VitalPatch RTM is another chest patch single lead ECG sensor intended for patients requiring longer term Holter monitoring. It is based off their previous device for remote vital signs monitoring and includes other parameters, like heart rate variability, respiratory rate and activity levels. Data is uploaded to cloud-based storage; thus, the device does not need to be shipped back for data analysis. The latter is reportedly facilitated by use of third-party AI analysis software (Cardiologs) and clinician overread. Data can be viewed in near real-time and an annotated interim report can be provided after 5 days of monitoring.

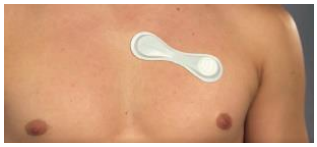

Figure 5. VitalPatch RTM.
VitalConnect, Inc.

The third-party software from Cardiologs is an FDA cleared AI-based software analysis platform that can detect 14 different arrhythmias from a broad array of monitoring devices as long as the data is in a compatible format. Shenzhen Carewell Electronics also has an FDA cleared AI-based ECG software analysis platform. Mayo clinic also has an AI software platform for ECG analysis in development.[15]

Non-ECG photoplethysmography (PPG)-based methods using wearable sensors, especially mHealth technologies, have also been developed for AF detection.[28-30] PPG is a technique using optical light-based methods to determine volume changes in the underlying microvasculature that occurs during the heartbeat. This technique is commonly used for measuring oxygen saturation (SpO2), but the PPG waveform can also be related to cardiac activity. For example, AF may be associated with varying pulse morphologies and pulse-to-pulse intervals. Deep learning based algorithms are expected to play a critical role in waveform analysis using these technologies.[29] FibriCheck is an example of one of the first FDA cleared PPG-based smartphone apps for AF detection. It utilizes the flash and camera for PPG waveform capture, so external sensors are not required. Another PPG-based technique uses the video camera to visualize subtle changes in skin coloration associated with changes in hemoglobin during the pulse cycle to create a PPG waveform.

Table 1. Types of Ambulatory ECG monitors.

Technology	Advantages and Disadvantages
Holter monitor	Inexpensive, widely available, good familiarity Multiple leads (up to 12 leads) similar to hospital-based ECG Typically short-term < 48 hours monitoring, best for frequent symptoms No real time analysis, device must be returned for data download and analysis Patient may not consistently record events and symptoms Electrodes and wires may cause discomfort, dissatisfaction May be taken off or fall off, patient reattachment difficulties
External loop recorder	Longer term recording up to a few months, may capture more infrequent events Captures only a short segment of ECG signal, manually or automatically activated Can capture short segments of ECG data from before event is registered Capability for wireless interim data download, analysis and alerts Non-invasive, small number of leads, electrodes may need to be reapplied over time Requires high degree of patient compliance and device interaction Requires specialized cardiac program management
Internal loop recorder	Longest monitoring option up to years, may better capture infrequent events Invasive implantation, but stable thereafter with no external wires/electrodes Most expensive upfront costs, requires periodic appointments for management Single lead configuration Capability for both automatic and patient-initiated event marking Requires specialized cardiac program management
mHealth event recorder	Records only short ECG segment after an event is detected Utilizes widely available smartphone technology and apps Multiple different wearable forms, including smartwatches and handhelds Good patient acceptance and satisfaction if tech savvy Real time alerts from AI-based programs for some arrhythmias Mostly single-lead configurations, lack of continuous data Electrodes are non-adhesive, improved patient comfort Diagnosis often requires confirmation with more advanced ECG methods
Patch monitors	Intermediate recording duration of a few weeks, continuous data Holter monitor like operation/management, but for longer duration Waterproof, requires little interaction after application, good patient acceptance May or may not require device return for data analysis Capability for wireless data download, interim reporting and alerts AI programs run on cloud-based data and specialized hardware Adhesive, single-lead configuration
Mobile cardiac telemetry	Short-term continuous remote data collection, good for high risk patients Data sent for analysis on a planned schedule, improves alarm capability Single or multiple (e.g. 3-lead) lead configurations possible AI can be used to improve event detection
Standalone AI platform	Cloud-based data analysis may be device agnostic AI programs run on specialized hardware may be more powerful, accurate Ability to detect more types of arrhythmia, facilitates workflow for clinician overread
PPG methods	Widely available, used mostly by low demand users Can be used with smartphone apps with no sensors required More advanced PPG sensors in smartwatches and fitness bands for pulse detection Indirect methods of waveform analysis may introduce false positives, negatives Requires confirmation using subsequent ECG-based techniques

Abbreviations: ECG=electrocardiogram, AI=artificial intelligence, PPG=photoplethysmography, mHealth=mobile and wireless health technologies

Clinical evidence summary

The Medline/PubMed bibliographic database and ClinicalTrials.gov database of registered clinical studies were searched in April 2021 to identify pivotal clinical evidence related to the use of novel ambulatory ECG monitoring devices and AI algorithms for arrhythmia analysis. Keywords used in the literature search strategy included*: artificial intelligence, machine learning, deep learning, ECG, arrhythmia, atrial fibrillation* and/or various product names. The following evidence summary is intended as a narrative review of select key clinical studies and is not intended as a comprehensive systematic review.

Overall, the literature search identified a very large body of published clinical evidence on mobile devices and/or AI algorithms for ambulatory ECG analysis. Various technologies had an evidence base ranging from a few pivotal studies to dozens of published clinical trials. For example, the Zio patch reports more than 30 peer-reviewed clinical studies. AliveCor reports device relevancy to more than 100 different publications. Smartphones/smartwatches have also been studied in more than 100 publications.[31]

There is also a large amount of published clinical literature available regarding deep learning applied to ECG analysis. One systematic review conducted in 2020 found 191 related research studies, with more than half published in the last year, suggesting very rapid development.[32] The most common deep learning architecture noted in publications was the convolutional neural network (CNN) followed by the CNN combined with the recurrent neural network (RNN).[33]

Supervised ML using large annotated ECG databases, such as the MIT-BIH arrhythmia database, PhysioNet dataset, Telehealth Network of Minas Gerais Brazil database, device-specific company-curated databases (e.g., iRhythm) and datasets collected at various hospitals and universities (e.g., Mayo Clinic, Cleveland Clinic, UC San Francisco, Huazhong University China) is currently the most common approach.[15] These training datasets range from tens of thousands of patients to millions of patients/ECGs.

A number of studies have demonstrated highly accurate, cardiologist-level arrhythmia diagnosis using deep neural networks (DNNs) for ECG analysis. For example, one study used the Zio patch and a DNN consisting of 33 convolutional layers and trained on 91,232 ECG records (iRhythm database) demonstrated an area under the curve (AUC) of 0.97 for classifying 10 different arrhythmias plus normal sinus rhythm or noise.[34] The diagnostic sensitivity and positive predictive value of the DNN reportedly exceeded that for 6 cardiologists interpreting the same ECGs. Similarly, a DNN trained on more than 2 million 12-lead ECG recordings (Brazil database) was shown to outperform a group of cardiology residents for diagnosing 6 types of arrhythmia.[35] Another CNN trained on 180,112 ECGs (Huanzhong database) was reportedly more accurate for diagnosing 21 different arrhythmias compared to a group of 53 cardiologists.[36]

In an example of hospital grade ECG interpretation, a CNN was trained on more than 1.7 million 12-lead ECG traces (Mayo database) with output of 66 different ECG codes and test descriptions similar to that provided by a cardiologist.[37] The AI analysis showed an AUC of ≥ 0.98 for 62 of the 66 ECG codes suggesting high agreement between the algorithm and cardiologist for the interpretation of a standard 12-lead ECG.

DNN methods have also been shown to outperform conventional ECG interpretation algorithms. For example, the Cardiologs DNN algorithm was shown to have better accuracy in detecting a major ECG abnormality compared to a conventional algorithm in ED patients.[38] For a diagnosis of AF in ED patients, the Cardiologs DNN outperformed the conventional algorithm and was as accurate as the conventional algorithm with physician overread (91% vs. 90%).[39]

Diagnostic yield is another important outcome for ambulatory ECG analysis. The 14-day Zio patch was shown to have a higher diagnostic yield than Holter monitoring in discharged ED patients with symptoms like palpitations, syncope and dizziness.[40-42] Further, in a pivotal randomized study (mSTOPS), patients at high risk of AF were found to benefit from immediate ECG monitoring with the Zio patch compared to delayed monitoring.[43] Patch monitoring led to higher rates of AF diagnosis at 4 months and 1-year compared to controls.

In a systematic review of the KardioMobile device, diagnostic yield rates ranged from 0.8% to ~36% depending on patient inclusion criteria and monitoring duration.[44]The Kardia device was also shown to have a higher diagnostic yield than an external loop recorder worn over a 2 to 4 week period.[45]

Beyond diagnosing AF as present or not present, there is an increasing clinical emphasis on determining the proportion of time spent in AF.[46] Patch devices may play a significant role in the diagnosis of AF burden. For example, in the KP-Rhythm study a threshold AF burden of 11.4% measured using the Zio patch was identified as an independent risk factor for stroke.[47] Used in conjunction with other risk factors, this could aid in decisions regarding anticoagulation therapy.

Opportunistic AF screening is a growing application for smart wearables. In a large pivotal trial (the Apple Heart study) enrolling 419,297 participants, the use of a PPG-based technique with a smartwatch detected potential AF in 0.52% of participants over 3 months of monitoring.[48] Subsequent ECG patch monitoring confirmed AF in about one-third of these cases. While the yield of this study was low, the entry requirements for patients who already had the technology were minimal. Regarding accuracy, a recent meta-analysis noted an AUC of 0.94 to 0.96 for diagnosis of AF using smartphones and smartwatches.[49] No difference was noted between those using PPG methods compared to ECG methods.

In patients with already diagnosed AF undergoing treatment, smart wearables are emerging as a potential means to optimize anticoagulation and/or rhythm control therapy.[50] For example, a pilot randomized study (iCare-AF) using the Alivecor Kardia device in patients with infrequent paroxysmal AF demonstrated the feasibility of intermittent anticoagulation based on daily smartphone rhythm monitoring.[51] In patients with persistent AF, ECG monitoring could also be used to confirm the need for cardioversion. In these cases, the availability of ECG monitoring can empower the AF patient to pursue an approach suitable to their unique presentation.

Beyond the diagnosis of arrhythmia, AI-based algorithms have the potential to diagnose other aspects of cardiac health. These applications utilize the capability of deep learning algorithms to distinguish subtle features in the ECG signal and non-linear relationships between the different features. A DNN trained on more than 1.5 million ECGs demonstrated an AUC of 0.85 to 0.9 for detection of hyperkalemia.[52] This model is undergoing FDA trials for potential use as a smartphone app for the detection of an electrolyte level without the need for a blood draw.

Another interesting AF surveillance application studied by the Mayo Clinic group showed the potential ability to detect AF by analyzing an ECG of normal sinus rhythm.[53] In other words, the patient didn't have to be in AF at the time AF was diagnosed from the ECG. Another study from the same group showed high accuracy for diagnosing asymptomatic left ventricular dysfunction from analysis of the ECG.[54] Clinically, this AI algorithm used in ED patients with dyspnea could provide a biomarker of heart failure as accurate or better than natriuretic peptide blood tests (NT-proBNP).[55] This DNN has also been shown to accurately predict patient gender and physiologic age from subtle features in the ECG.[56]

Financial issues

For short-term ambulatory ECGs, Holter monitoring is typically the lowest cost option, with device and set-up costs around $100 and total cost of diagnosis of about $175 for 2 days of wear.[57] Intermediate duration single-lead patches may cost on the order of ~$300 to $350 including the sensor and analysis for up to 14 days of wear. Implantable loop recorders may cost >$2,000 for the device and an additional cost for the implantation procedure. These may incur periodic analysis and visit charges with wear up to 3 years.

Smartphone-based devices like Kardia cost about $89 for the single-lead and $149 for the 6-lead sensor. Basic storage and analysis may be included, with advanced support and analysis costing around $10/month with a membership. Smartwatches may cost about $300 and up. Features like ECG and AF detection may be free on smartwatches and included with built-in health monitoring apps used for data storage and analysis. Some PPG techniques requiring no external sensors and using smartphone apps may cost <$4.99 for one-time purchase.

The cost-effectiveness of various ambulatory ECG monitoring technologies is predicated on yielding a definitive diagnosis as early as possible so that effective treatment can be initiated. For example, early diagnosis of AF triggers initiation of anticoagulation therapy that prevents stroke; thus, improving outcomes and quality of life (QOL) and saving on associated future resource utilization and costs. Due to the high morbidity, mortality and costs associated with stroke, a large number of ambulatory ECG monitoring options may be deemed cost-effective.[57-64]

These findings, however, tend to be highly dependent on the timing, comparator and model assumptions. Diagnostic yield tends to increase with a longer duration of monitoring, but the incremental yield diminishes significantly for each week after initiation of monitoring. For example, about one-third of arrhythmias may occur after 48 hours, but most may occur by 8 days. Diagnostic yield also is a function of patient criteria. Older patient (e.g., > 75 years) and those with risk factors may have a higher incidence of AF and likelihood of detection using AF screening technologies. Holter monitoring is the most common comparator, but there are relatively few comparisons to mHealth and patch devices. Therefore, further cost-effectiveness studies of these alternatives are needed.

Some specific cost-effectiveness data are available for Kardia, Zio patch and mHealth devices.[25, 65-68] A study of community monitoring for potential AF noted the use of Kardia could avoid the need for and costs associated with serial 12-lead ECG monitoring.[65] An economic model of the Zio patch suggested its use could avoid 10.8 more strokes annually and provide direct savings of more than $150,000 in one setting.[67] Further cost modeling by the UK National Institute for Health and Care Excellence (NICE) found the Zio patch could be cost saving if Holter monitoring or other ambulatory event recorder options were repeated due to negative results, assuming the Zio patch did not need to be repeated. PPG-based AF detection could also lead to cost-effectiveness due to reduced strokes and associated costs.[66]

Direct third-party payer reimbursement is an evolving issue. In a significant development for patch devices, the Centers for Medicare and Medicaid Services (CMS) published a final rule for 2021 in the Medicare Physician Fee Schedule (MPFS). This rule established payment policies falling under a new set of Current Procedural Terminology (CPT®) codes for continuous ambulatory ECG monitoring (CPT codes 93241-93248). These codes are delineated by wear time as between 48 hours and 7 days or between 7 days up to 15 days. These codes will likely be adopted by most payers in 2021.

The MPFS final rule, however, did not set a national payment rate for the patch devices. Therefore, rates are set by individual regional Medicare Administrative Contractors (MACs). In April 2021, one MAC (Novitas) reported that it had lowered patch monitoring reimbursement under the new codes from $310 to $103-$115. Notably, this rate may not cover the device cost and thus may limit usage in patients covered by this payer. Renegotiation of these rates is reportedly underway in 2021. Other payer rates may vary and patients may be required to pay some portion of costs as well.

CPT codes 93224-93228 are typically used for Holter monitoring up to 48 hours in duration. For intermittent external devices (e.g. external loop recorders), CPT codes 93268-93272 may apply. MCT uses CPT codes 93228 and 93229 and internal loop recorders may use CPT codes 93291-93299.

Some reimbursement scenarios for mHealth devices may fall under payment policies for remote monitoring. CMS pays for RM using CPT codes 99453-99458 and 99091. Again, payment rates vary, but average CMS reimbursement may provide about $21 for RM set-up, $69 for RM devices, ~$54 per month for interactive patient management and ~$60 per month for data analysis and interpretation.

Patient selection criteria

Due to its rapidly emerging nature, patient selection for the use of some of the newer devices covered in this report are not yet established. Important sources to inform patient selection may include specific FDA cleared product labeling, professional society guidelines and patient inclusion/exclusion criteria from pivotal trials.[5, 69-71] Unfortunately, guidelines often cover technology in a broad sense and are usually not device specific. Strong evidence from pivotal trials is also sparse.

Due to unknowns, conservative patient selection may be warranted. Further, institutional and clinician monitoring of device accuracy and utility may be needed to ensure quality care. If possible, usage for not well-established indications should be part of a clinical research study with publication of results to help with future usage decisions.

Some common use cases for ambulatory ECG monitoring may include:

- Evaluation of recurrent unexplained episodes of presyncope, syncope, palpitations or dizziness caused by suspected arrhythmia
- For suspected arrhythmia in persons with a non-diagnostic Holter monitor
- For a suspected arrhythmia when symptoms occur infrequently (e.g., less than daily) and it is unlikely to be detected by Holter monitoring
- For MCT when patients require more frequent arrhythmia analysis during ECG monitoring
- Evaluation of suspected AF as a cause of cryptogenic stroke
- For monitoring anti-arrhythmic drug therapy or ablation response
- To document arrhythmia burden in AF
- Screening for AF

In these cases, newer technologies may be carefully considered as a substitute for conventional ambulatory ECG monitoring technologies.

Future developments

Typical of an early phase emerging technology, wearable connected devices and AI analysis are currently in a period of rapid growth in their clinical evidence base. Many further clinical studies are currently underway that will help to better define accuracy, clinical utility and cost-effectiveness of the different ambulatory ECG devices. Independently-conducted, non-manufacturer sponsored studies are particularly needed to corroborate current evidence and “real-world” studies in different use cases are also in progress. Due to rapid developments, efforts should be made to update the literature review included in this report.

Continual incremental improvement in technology is occurring. Trends in technology miniaturization, extended battery life, solid state memory capacity, high-speed communication technology and sensor design favor the development of even smaller, more comfortable, longer-lasting devices with more capabilities. The utilization of smartphones in healthcare is a megatrend expected to drive explosive growth of mHealth technologies used in ambulatory ECG monitoring.

Improvement in AI-related algorithms has also resulted from advances in fast, inexpensive parallel processing hardware, availability of large and growing annotated datasets, more widespread availability of AI programming tools and refinement of AI programming techniques using deep learning. These trends will undoubtedly continue and may be expected to improve diagnostic accuracy.

Emerging RM devices and platforms are incorporating sensors for many more physiologic parameters beyond the ECG. All of the vital signs (heart rate, blood pressure, body temperature, respiratory rate) and other parameters (e.g., oxygen saturation, cardiac output, heart rate variability, heart sounds) commonly measured in the cardiology clinical can be incorporated into newer devices. In addition, they may also monitor sleep quality, exercise and activity levels. Capability to record weight, symptoms, medication adherence and diet may also be available. Collecting those parameters with clear targets or thresholds directly applicable in evidence-based treatment algorithms may be expected to result in the best outcomes. As more and more data from multiple parameters are collected, automated approaches using AI algorithms may be critical to assist a timely review of the physiologic data.

An exciting area of future development involves the use of deep learning methods to identify new “biomarkers” of disease. The processing power of deep learning excels at determining subtle and non-linear relationships in large datasets. Some applications include diagnosing AF or heart failure development from subclinical disease, predicting patient risk and prognosis and directing and monitoring response to therapy. Instilling confidence in these biomarkers, however, will require better methods of interpretability of AI algorithms. This is an active area of future research.

Summary and recommendations

The following summary and recommendations are based on the material presented in this report:

- Continuous remote patient monitoring is an evolutionary next step in the healthcare delivery paradigm. Fast-moving developments in wearable sensors and mHealth technologies are driving rapid growth. Changes in patient demographics and the utilization of value-based reimbursement scenarios also portend more use of RM. Because of this, hospitals and health systems should be pro-actively involved in exploring new ambulatory RM technology and applications.

- Ambulatory ECG monitoring utilizing wearable sensors, smartphones, mHealth apps, smartwatches and patches are now widely commercially available. Many of these devices have received FDA clearance and many more are in the pipeline. These devices are capable of on-demand event recording, continuous ECG data collection and/or intermittent wireless data upload. They have been shown to reliably capture a high-quality ECG signal for analysis.
- Comfort, convenience, availability, ease-of-use and patient satisfaction are some of the main advantages of these new ambulatory ECG technologies. These characteristics are hallmarks of disruptive innovation and may drive adoption in spite of device and evidence limitations. Initial adoption may be more prevalent in low demand users, but as they mature, they can be expected to realize more traditional healthcare applications.
- After the ECG signal is collected, it must be read and analyzed. Technologies that employ AI and machine learning are becoming very common for these tasks. Some simple arrhythmia diagnosis, like AF, can be performed by AI algorithms in real-time. More comprehensive ECG analysis can be performed by deep learning algorithms operating on cloud-based data. The primary application of these AI programs is to flag and triage findings for clinician overread; thus, optimizing clinical workflow and reducing physician workload.
- The potential accuracy of select AI algorithms for diagnosing arrhythmia has been shown in a number of studies. High sensitivity, specificity and AUC have been reported. For highly controlled conditions and ECG datasets, AI programs have even outperformed clinician-based diagnosis. Used as an adjunct tool in combination with clinician judgment, accuracy may be expected to be even greater. Though promising, most of the newly emerging devices require further studies to better define their diagnostic accuracy and clinical impact.
- AF is one of the most targeted applications for these technologies. This is a high-impact indication with demonstrated need for improvement. New technologies incorporating wearable ECG sensors with AI analysis have shown increased AF diagnostic yield with the potential for better treatment, improved patient outcomes and cost-effectiveness. Hospitals should examine their current AF detection paradigms and incorporate these newer technologies where appropriate.
- There are many different alternatives available. Appropriate technology selection should consider FDA status and labeling, accuracy data, clinical outcome evidence, cost-effectiveness and user-friendliness. Technologies that are difficult to use will reduce compliance and therefore effectiveness, as well as decrease patient satisfaction. Patient factors to consider include clinical status, risk stratification, symptom frequency and the patient's social circumstances and technology savvy. Implementation may need to consider hospital information technology infrastructure, current programs for RM in chronic diseases and local clinical experience and availability.
- The use of AI, wearables and mHealth technologies is currently in the process of transforming the clinical pathways for ambulatory cardiac care. The timing of this paradigm change, however, may be affected by restrictive reimbursement policies, government regulations and legal/liability issues. Hospitals implementing these technologies at this early adopter phase will need to work through these barriers and implementation challenges. However, those that do may be best positioned to take advantage of the revolution as it becomes more and more mainstream.

Related links

CMS policy: MPFS

FDA resources: 510(k) database search, SAMD, AI/ML software, mobile medical applications

Research articles: PubMed Central, Google scholar

Select manufacturer websites: AliveCor Kardia, iRhythm Zio, Apple Watch, Fitbit Sense, Galaxy Watch3, Preventice BodyGuardian, Bardy CAM, Philips ePatch, VitalConnect VitalPatch RTM, Cardiologs

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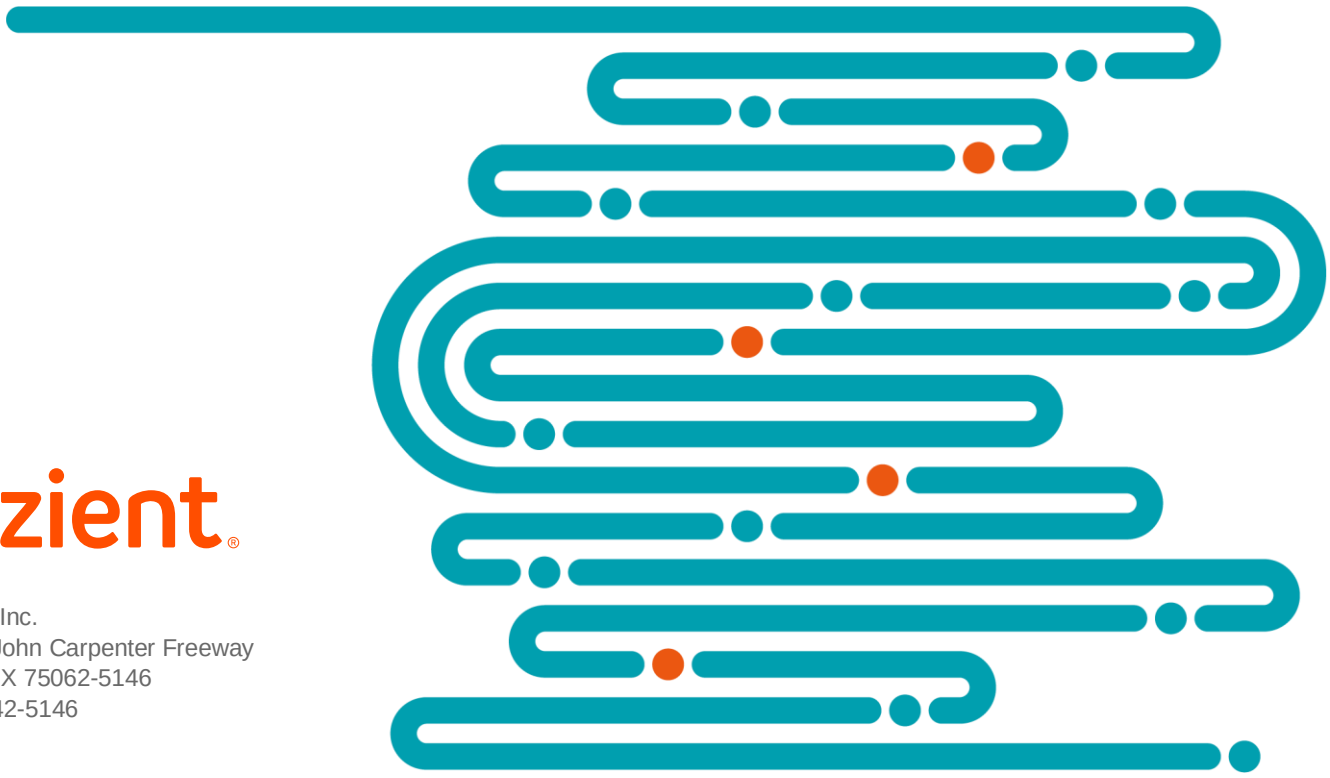

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